Exhibit 1

S.M. Moskowitz et al., *CFTR-Related Disorders*, Gene Reviews, last revision August 24, 2005, *available at* http://www.geneclinics.org/servlet/access?db=geneclinics&id=8888889&key=hTAmeSXYiaUo1&gry=INSERTGRY&fcn=y&fw=IRVN&filename=/profiles/cf/details.html.

Funded by the NIH • Developed at the University of Washington, Seattle

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CFTR-Related Disorders

[Includes: Cystic Fibrosis (CF, Mucoviscidosis) and Congenital Bilateral Absence of the Vas Deferens (CBAVD)]

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Initial Posting: **26 March 2001**
Last Revision: **24 August 2005**

Summary

Disease characteristics. *CFTR*-related disorders include cystic fibrosis (CF) and congenital bilateral absence of the vas deferens (CBAVD). Cystic fibrosis affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. Affected individuals have lower airway inflammation and chronic endobronchial infection, progressing to end-stage lung disease characterized by extensive airway damage (bronchiectasis, cysts, and abscesses) and fibrosis of lung parenchyma. Meconium ileus occurs at birth in 15-20% of individuals diagnosed with CF. Pancreatic insufficiency with malabsorption occurs in the great majority of individuals with CF. More than 95% of males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic Wolffian duct structures. CBAVD occurs in men without pulmonary or gastrointestinal manifestations of CF. Affected men have azoospermia and are thus infertile.

Diagnosis/testing. Most commonly the diagnosis of cystic fibrosis (CF) is established in individuals with one or more characteristic phenotypic features of CF plus evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function based upon ONE of the following: presence of two disease-causing mutations in the *CFTR* gene OR two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L) OR transepithelial nasal potential difference (NPD) measurements characteristic of CF. The American College of Medical Genetics has recommended a

panel of 23 common alleles. The *CFTR* mutation detection rate varies with ethnic background. In some symptomatic individuals, only one or neither disease-causing mutation is detectable; in some carriers, the disease-causing mutation is not detectable. The diagnosis of *CFTR*-related CBAVD is established in males with azoospermia, low volume of ejaculated semen, absence of vas deferens on clinical or ultrasound examination, and at least one disease-causing mutation in *CFTR*.

Genetic counseling. *CFTR*-related disorders are inherited in an autosomal recessive manner. Sibs of a proband with cystic fibrosis and brothers of a proband with CBAVD have a 25% chance of being affected, a 50% chance of being asymptomatic carriers, and a 25% chance of being unaffected and not carriers. Molecular genetic testing for disease-causing mutation(s) in the *CFTR* gene is used for carrier detection in population screening programs. Prenatal testing is available for pregnancies at increased risk for *CFTR*-related disorders.

Diagnosis

Clinical Diagnosis

Cystic Fibrosis

Phenotypic features of CF include, but are not limited to the following:

- **Chronic sinopulmonary disease** (chronic cough and sputum production, chronic wheeze and air trapping, obstructive lung disease on lung function tests, persistent colonization with pathogens commonly found in individuals with CF, chronic chest radiograph abnormalities, digital clubbing)
- **Gastrointestinal/nutritional abnormalities** (malabsorption/pancreatic insufficiency, distal intestinal obstructive syndrome, rectal prolapse, recurrent pancreatitis, meconium ileus, chronic hepatobiliary disease, failure to thrive, hypoproteinemia, fat-soluble vitamin deficiencies)
- **Obstructive azoospermia**
- **Salt-loss syndromes** (acute salt depletion, chronic metabolic alkalosis)

The diagnosis of cystic fibrosis (CF) is established in individuals with the following:

- One or more characteristic phenotypic features of CF
  AND
- Evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function based upon ONE of the following:
  - Presence of two disease-causing mutations in the *CFTR* gene
    OR

- Two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L)
  OR
- Transepithelial nasal potential difference (NPD) measurments characteristic of CF

The diagnosis of CF may be made in the absence of phenotypic features of CF in the following settings:

- Confirmed diagnosis of CF in a sib and an abnormal sweat chloride value or the presence of the same two disease-causing mutations in the *CFTR* gene as identified in an affected sib
- Diagnosis in a newborn screening program (based on the presence of two disease-causing mutations in the *CFTR* gene OR abnormal sweat chloride value). In 2002, 12.8% of newly diagnosed individuals were identified through newborn screening [CFF Patient Registry 2002].
- In utero diagnosis by presence of two disease-causing mutations in the *CFTR* gene. In 2002, 4.0% of newly diagnosed individuals were identified by prenatal diagnosis [CFF Patient Registry 2002].

CBAVD

The diagnosis of *CFTR*-related congenital bilateral absence of the vas deferens (CBAVD) is established in males with the following:

- Azoospermia (absence of sperm in the semen)
- Absence of the vas deferens on palpation (Rarely, a thin fibrous cord representing a rudimentary vas deferens may be present.)
- An identifiable mutation in one or both *CFTR* alleles [Dork et al 1997]

Additional features that may be seen include the following:

- A low volume of ejaculated semen (<2 mL; normal: 3-5 mL) with a specific chemical profile
- Evidence of abnormalities of seminal vesicles or vas deferens upon rectal ultrasound examination

Testing

Cystic Fibrosis

Sweat chloride. The National Committee for Clinical Laboratory Standards has published guidelines for the appropriate performance of the quantitative pilocarpine iontophoresis procedure [Wayne 1994 , Legrys 1996]. Centers accredited by the Cystic Fibrosis Foundation are required to adhere to this protocol; alternative sweat test procedures are not acceptable. A minimum sweat weight of 75 mg must be collected during a 30-minute period to assure a sweat rate of 1 g/M ^{2}/min. A chloride concentration of greater than 60 mEq/L in sweat on two separate occasions is diagnostic. This test is positive in over 90% of individuals with CF.

- Sweat chloride levels higher than 160 mEq/L are not physiologically possible and should be attributed to technical error.
- False positive sweat chloride results may be associated with other conditions, most notably mucopolysaccharidosis I-H (Hurler syndrome).
- False negative sweat chloride results may be obtained in the setting of acute CF-related salt losses.
- When CF is suspected in an individual with hyponatremia and hypochloremia, sweat testing should be deferred until electrolytes have been repleted and fluid status stabilized.

Transepithelial nasal potential difference (NPD). Respiratory epithelia regulate ion transport and alter content of the airway surface fluid by active transport mechanisms. The absence of functional CFTR at the apical surface with resultant alterations in chloride efflux and sodium transport produces an abnormal electrical potential difference across epithelial surfaces. The protocol for NPD measurements in individuals over six years of age is well described, standardized, and safely performed in many specialized CF centers worldwide [Knowles et al 1995]. Compared to individuals who do not have CF, individuals with CF have the following:

- A raised (more negative) baseline NPD reflecting enhanced sodium absorption across a relatively chloride-impermeable membrane.
- A greater change in NPD during perfusion of the nasal mucosa with amiloride, an inhibitor of sodium channel activity.
- Minimal change in NPD in response to perfusion with amiloride/low chloride/beta-agonist, as a measure of cAMP-mediated chloride transport via CFTR.

Newborn screening. Newborn screening has been implemented in some states using immunoreactive trypsinogen (IRT) assays performed on blood spots [National Newborn Screening Status Report (pdf)]. Trypsinogen is synthesized in the pancreas; in CF, its release into the circulation appears to be enhanced by abnormal pancreatic duct secretions. Thus, IRT levels are elevated in cystic fibrosis. In keeping with the use of IRT as a screening test, the definition of a positive result favors sensitivity over specificity, resulting in a decreased positive predictive value and a significant false positive rate when IRT is used by itself. Abnormal results are therefore further evaluated with molecular genetic testing of the *CFTR* gene OR sweat testing after the child is at least two months of age (if two disease-causing mutations are not identified) [Gregg et al 1997 , Pollitt 1998].

CBAVD

Semen analysis. Additional findings in the semen of men with CBAVD include low pH (pH <7; normal: pH >8); elevated citric acid concentration (>2000 mg/100 mL; normal: 400-1500 mg/100 mL); elevated acid phosphatase concentration (760-1140 mμ/mL; normal: 140-290 mμ/mL); low fructose concentration (30-80 mg/100 mL; normal 250-720 mg/100 mL); and failure to coagulate [Holsclaw et al 1971].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is

listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work; listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —ED.

Gene. *CFTR* is the only gene known to be associated with the *CFTR*-related disorders, cystic fibrosis and CBAVD. More than 1000 mutations have been identified in the *CFTR* gene; most are rare, having been detected in only one family.

Molecular genetic testing: Clinical uses

- Diagnosis in symptomatic individuals
  - Cystic fibrosis
  - CBAVD
- Carrier testing
  - In at-risk relatives and their reproductive partners
  - In population screening programs for CF
- Prenatal diagnosis
  - For pregnancies at increased risk for CF
  - For pregnancies in which fetal echogenic bowel has been identified

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**
  - **Mutation panels.** Several panels are available. In 2004, the American College of Medical Genetics (ACMG) decreased the recommended mutation panel from 25 to 23 mutations [Watson et al 2004]. The mutation detection rate for the 23-mutation panel (Table 8) varies with ethnic background (Table 1) [Richards et al 2002].
  - **5T/TG tract analysis**
    - The Poly T tract, a string of thymidine bases located in intron 8 of the *CFTR* gene, can be associated with *CFTR*-related disoders depending on its size. The three common variants of the poly T tract are 5T, 7T, and 9T. Both 7T and 9T are considered polymorphic variants and 5T is considered a variably penetrant mutation. The 5T variant is thought to decrease the efficiency of intron 8 splicing. Poly-T testing is appropriate as a reflex test when a R117H mutation is detected or an adult male is being evaluated for CBAVD.
    - The TG tract lies just 5' of the poly T tract. It consists of a short string of TG repeats that commonly number 11, 12 or 13. A longer TG tract (12 or 13) in conjunction with a shorter T tract (5) has the strongest adverse effect on proper intron 8 splicing [Cuppens et al 1998 , Groman et al 2004].
    - Males with CBAVD or suspected CBAVD, individuals with non-classic CF,

or adult carriers of 5T who wish to further refine their reproductive risks are all appropriate for T/TG tract typing.

- **Duplication/deletion analysis.** Multiplex-ligation-dependent probe amplification (MLPA) can detect deletions not identified by sequence analysis. Mutation detection rate is not known.

- **Sequence analysis.** Sequencing of all exons, intron/exon borders, promoter regions and specific intronic regions detects more than 98% of *CFTR* mutations [Strom et al 2003].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *CFTR*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Rate by Population Group		Test Availability
Targeted mutation analysis	*CFTR* mutations using the original 25-mutation panel [1]	Ashkenazi Jewish	97% [2]	Clinical Testing
		Non-Hispanic Caucasian	88.3% [3]	
		African American	69% [2]	
		Hispanic American	57% [2]	
		Asian American	Unknown	
	MPLA: *CFTR* deletions	All populations	Unknown	
Sequence analysis	*CFTR* sequence alterations	All populations	98.7% [4]	

1. The original 25-mutation panel recommended by the American College of Medical Genetics [Grody et al 2001] included the mutations listed in Table 8 and 1078delT and I148T. The 23-mutation panel recommended in 2004 is expected to have a similar mutation detection rate. Other panels may have significantly different mutation detection rates.
2. Grody et al 2001
3. Palomaki et al 2002
4. Using an assay to sequence all the coding sequences, splice donor and acceptance sites, the promotor region and two intronic sequences [Strom et al 2003]

Interpretation of test results used in diagnosis of individuals suspected of having CF

- For issues to consider in interpretation of sequence analysis results, click here .
- The number of abnormal alleles detected (two, one, or none) (Table 2) depends on the mutation detection rate (Table 1).

Table 2. Expected Percentage of Abnormal Alleles Detected in Individuals

with CF Based on the Detection Rate of the Test Method Used

Mutation Detection Rate	Percentage of CF Population for which a Given Number of Abnormal Alleles Will Be Identified		
	Both Abnormal Alleles	One Abnormal Allele	Neither Abnormal Allele
98%	96%	4%	0%
95%	90%	10%	0%
90%	81%	18%	1%
85%	72%	26%	2%
80%	64%	32%	4%
75%	56%	38%	6%
70%	49%	42%	9%
60%	36%	48%	16%
50%	25%	50%	25%
40%	16%	48%	36%
30%	9%	42%	49%

Calculated using Hardy-Weinberg Rule

Interpretation of test results used in diagnosis of individuals suspected of having CBAVD. The percentage of mutant *CFTR* alleles and 5T variant alleles detected in males with CBAVD is summarized in Table 3 .

Table 3. The Percentage of Abnormal Alleles Detected in Males with CBAVD[1]

Molecular Genetic Test Result		% of Individuals with CBAVD
# of Mutant *CFTR* Alleles Other than 5T	# of 5T Alleles	
2	0	26%
0	2	2%
1	1	26%
1	0	17%
0	1	8%
0	0	22%

1. Based on pooled data from Dork et al 1997 , Mak et al 1999 , Casals et al 2000 , and Wang et al 2002

Interpretation of results of CF carrier testing. It is recommended that in

population screening programs cystic fibrosis carrier testing be performed using the ACMG 23-mutation panel (Table 8).

- 5T and TG tract typing should not be included in a routine carrier screen.
  - If an individual has the R117H mutation, reflex testing for the variants 5T/7T/9T is recommended. If the individual has the 5T allele, family studies are recommended to determine if the 5T allele is in cis configuration or trans configuration with the R117H allele.
- The 5T/TG tract analysis is not able to provide a specific risk figure for developing symptoms or having a child who develops symptoms of non-classic CF or CBAVD; it is able to assign risk as "increased" or "decreased." A person with ΔF508 and 5T/11TG is less likely to develop non-classic CF, but it is still possible. Conversely, an individual with ΔF508 and 5T/13TG is more likely, though not certain, to develop non-classic CF or CBAVD [Groman et al 2004].

Testing Strategy for a Proband

Cystic Fibrosis

In most circumstances, the following strategy is indicated:

- Quantitative pilocarpine iontophoresis for sweat chloride concentrations (remains the primary test for the diagnosis of CF, accurately diagnosing >90% of cases)
- Molecular genetic testing of *CFTR* for diagnostic purposes if sweat chloride testing is unavailable or uninformative *(CFTR* molecular genetic testing for prognostic and epidemiologic purposes is appropriate for individuals diagnosed with CF based on sweat chloride testing.)
- Transepithelial nasal potential difference (NPD) measurements to confirm the diagnosis of CF in symptomatic individuals with borderline/nondiagnostic sweat tests in whom two *CFTR* disease-causing mutations have not been detected

In the following special circumstances, *CFTR* molecular genetic testing is the initial diagnostic test:

- Prenatal testing, in a high-risk fetus
- Prenatal diagnosis in low-risk fetus with echogenic bowel
- Newborn screening
- Symptomatic infants (i.e., those with meconium ileus) who are too young to produce adequate volumes of sweat.
- Testing of symptomatic sibs of an affected individual in whom both *CFTR* mutations have been identified

CBAVD

The diagnosis of CBAVD is generally made in three steps:

1. Evaluation of infertility: A male with severe oligospermia (<5 million), azoospermia, or very low volume of semen (<2 mL) proceeds to Step 2.
2. The male is evaluated clinically by a urologist. If absence of the vas deferens is

diagnosed by palpation, the workup proceeds to Step 3. (Imaging may be used but is not usually necessary if the clinical examination is consistent.)
3. The male is evaluated for *CFTR* mutations.

Genetically Related (Allelic) Disorders

An increased prevalence of *CFTR* mutations has been noted in individuals with idiopathic pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis. The reader is referred to the following references for further information: Zielenski & Tsui 1995 , Cohn et al 1998 , Luisetti et al 1998 , Mickle & Cutting 1998 , and Wang et al 2000 .

Clinical Description

Natural History

Cystic Fibrosis

CF affects the epithelia in several organs resulting in a complex, multisystem disease that includes the exocrine pancreas, intestine, respiratory tract, male genital tract, hepatobiliary system, and exocrine sweat glands. Individuals with CF and pancreatic sufficiency (<10%) have a milder clinical course with greater median survival (i.e., 56 years [1995 CFF Patient Registry]) than those with pancreatic insufficiency. The great majority of individuals with CF are pancreatic insufficient. The overall median survival is 31.6 years [CFF Patient Registry 2002]. A gender difference is present in CF with greater median survival in males than in females [CFF Patient Registry 1999]. Disease expression varies by severity of *CFTR* mutations [Gan et al 1995 , De Braekeleer et al 1997], genetic modifiers [Garred et al 1999 , Zielenski et al 1999], and environmental factors [Rubin 1990]. The range extends from early childhood death as a result of progressive obstructive lung disease with bronchiectasis, to pancreatic insufficiency with gradually progressive obstructive lung disease during adolescence and increasing frequency of hospitalization for pulmonary disease in early adulthood, to recurrent sinusitis and bronchitis or male infertility in young adulthood.

Respiratory. Pulmonary disease remains the major cause of morbidity and mortality in CF [CFF Patient Registry 2002]. Affected individuals have lower airway inflammation and chronic endobronchial infection. Failure of lung defenses lead to bacterial endobronchitis (most commonly *Staphylococcus aureus* and *Pseudomonas aeruginosa*) with resulting airway obstruction and intense neutrophilic inflammation. Early manifestations are chronic cough, intermittent sputum production, and exertional dyspnea. As the lung disease progresses as a result of chronic endobronchitis, structural injury to the airways occurs with resulting bronchiectasis. End-stage lung disease is characterized by extensive damage to the airways (cysts/abscesses) and accompanying fibrosis of lung parenchyma adjacent to airways.

Gastrointestinal

- Meconium ileus occurs in 15-20% of individuals diagnosed with CF.
- Pancreatic insufficiency with malabsorption occurs in the great majority of

individuals with CF. (92% of individuals with CF in the 2002 CFF Patient Registry were taking pancreatic enzyme supplements.) Exocrine pancreatic insufficiency is caused by inspissation of secretions within the pancreatic ducts and ultimately interstitial fibrosis. The clinical manifestations are steatorrhea and poor growth related to fat malabsorption and hemolytic anemia, defective coagulation, or skin rashes related to deficiencies of fat-soluble vitamins and zinc.

- Cystic fibrosis-related diabetes mellitus (CFRDM) may present in adolescence; 3.1% of children under 18 years of age require insulin. The prevalence increases in adulthood with more than 17% of individuals over 18 years of age requiring insulin [CFF Patient Registry 2002]. The etiology is a combination of reduced insulin secretion (secondary to fibrosis of the pancreas and reduced number of islet cells) and peripheral insulin resistance [Lanng 1996 , Hardin et al 1997].
- Hepatobiliary disease, with elevation of serum concentration of liver enzymes in school-age children, infrequently progresses to biliary cirrhosis in adolescents and adults. Prevalence of liver disease varies based on definition, with the overall rate reported as 6.1% in the 2002 CFF Patient Registry . As liver disease progresses, individuals develop portal hypertension and varices. Liver disease is second to pulmonary disease (plus organ transplantation complications) as a cause of mortality in CF (1.7% of deaths) [CFF Patient Registry 2002].

Fertility

- More than 95% of males with CF are infertile as a result of azoospermia caused by altered vas deferens, which may be absent, atrophic or fibrotic. The body and tail of the epididymis and seminal vesicles may be abnormally dilated or absent.
- Women with CF are fertile, although a few females have abnormal cervical mucus that may contribute to infertility. The rate of live births among females with CF age 13-45 years is 1.9 per 100 [CFF Patient Registry 2002].

Congenital Bilateral Absence of the Vas Deferens

Men without pulmonary or gastrointestinal manifestations of CF may have CBAVD. Absence of the vas deferens does not pose a health risk per se to the affected male. Testicular development and function and spermatogenesis are usually normal. Bilateral absence of the vas deferens is generally identified during evaluation of infertility or as an incidental finding at the time of a surgical procedure, such as orchiopexy. Hypoplasia or aplasia of the vas deferens and seminal vesicles may occur either bilaterally (CBAVD) or unilaterally (CUAVD).

Genotype-Phenotype Correlations

Probands

Cystic fibrosis. The best correlation between genotype and phenotype is seen in the context of pancreatic function. The most common mutations have been classified as pancreatic sufficient ("PS") or pancreatic insufficient ("PI") (see Table 9 below). Individuals with pancreatic sufficiency usually have either one or two PS alleles, indicating that PS alleles are dominant with respect to pancreatic phenotype.

In contrast, genotype-phenotype correlation is generally poor for pulmonary disease in CF. Pulmonary disease among individuals with identical genotypes varies widely, a finding that may be accounted for in part by genetic modifiers or environmental factors. However, compound heterozygotes with ΔF508/A455E have better pulmonary function than individuals who are homozygous for ΔF508 [Gan et al 1995 , De Braekeleer et al 1997]. In addition, the severity of lung disease in individuals with one or two R117H mutations depends upon the presence of a variation in the poly T tract of intron 8 [Kiesewetter et al 1993 , Massie et al 2001]. Individuals with a *CFTR* disease-causing mutation plus the 5T variant in cis configuration with the R117H mutation usually develop the lung disease of CF, but those individuals with R117H and the 7T variant or the 9T variant have a highly variable phenotype, that can range from no symptoms to mild lung disease (Kiesewetter et al 1993 , Chmiel et al 1999). Because A455E and R117H mutations are associated with pancreatic sufficiency, the less severe lung disease seen in individuals with these mutations could be the consequence of better nutritional status.

CBAVD. CBAVD usually results from the combination of one severe CF mutation on one chromosome with either a mild CF mutation or the 5T allele on the other chromosome (Table 3). However, some overlap exists between the CBAVD phenotype and a very mild CF phenotype, with some fraction of individuals with CBAVD also reporting respiratory or pancreatic problems [Dork et al 1997 , Gilljam et al 2004]. Moreover, the 5T allele may be associated with lung disease in adult females with CF-like symptoms (Noone et al 2000). Thus, caution must be exercised in attempting to use genotype to predict the future course of individuals initially diagnosed with CBAVD only.

At-risk individuals. Genotype-phenotype correlations are most relevant for genetic counseling of two carriers who have not had an affected child but who have been detected either through evaluation of at-risk family members or screening programs. The considerations in predicting the phenotype of potential offspring are the same as described above for CF and CBAVD probands. In general, prediction of severity of pancreatic disease on the basis of genotype is most reliable, while prediction of the severity of respiratory disease is less reliable. Prediction of the risk of CBAVD from genotype is reasonably reliable, but couples should be aware that mild respiratory and/or pancreatic disease can also occur in individuals with genotypes usually associated with CBAVD. The mechanism of partial penetrance of the 5T allele for CBAVD appears to be variation in the length of the adjacent TG tract (estimated at 60% in one study [Zielenski & Tsui 1995]).

Table 4. Genotype-Phenotype Correlations

CFTR Genotype [1]		Range of Phenotypes [2]
First Allele	**Second Allele (or Homozygous)**	
Classic (e.g., ΔF508)	Classic	Classic >> non-classic
Mild (e.g.,		

A455E)	Classic or mild	Non-classic > classic
R117H/5T	Classic or mild	Non-classic > classic
R117H/7T	Classic or mild	Asymptomatic female or CBAVD > non-classic
5T/TG13 or TG12	Classic or mild	CBAVD or non-classic CF >> asymptomatic carrier
5T/TG11	Classic or mild	Asymptomatic > CBAVD
7T or 9T	Classic or mild	Asymptomatic
7T or 9T	7T or 9T	Asymptomatic

1. Patterns reflect dominant effect of "milder" alleles in compound heterozygotes. Classic alleles generally refer to Class I-III mutations; mild alleles refer to Class IV-V mutations exclusive of R117H and 5T alleles (see Table 10).
2. Data derived from Kiesewetter et al 1993 , Witt et al 1996 , Brock et al 1998 , Cuppens et al 1998 , Mak et al 1999 , Wang et al 2002 , McKone et al 2003 , Groman et al 2004

Prevalence

CF is the most common life-limiting autosomal recessive disorder in the Caucasian population. The disease incidence is one in 3200 live births among Caucasians [Rosenstein & Cutting 1998]. Approximately 30,000 affected persons live in the US. In the Caucasian population, the heterozygote frequency is one in 22-28. Cystic fibrosis occurs with lower frequency in other ethnic and racial populations (one in 15,000 African-Americans, and one in 31,000 Asian Americans) [Rosenstein & Cutting 1998].

Table 5. Carrier Frequency for Mutant *CFTR* Alleles

Population Group	Approximate Carrier Frequency	Reference
Ashkenazi Jewish	1/29	Kerem et al 1997
North American Caucasian	1/28	Hamosh et al 1998
African American	1/61	Hamosh et al 1998

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Cystic fibrosis needs to be considered in the following:

- Infants with meconium ileus
- Infants with hyponatremia and hypochloremia of unknown etiology with compensatory metabolic alkalosis
- Infants with hypoproteinemia and anemia
- Children with rectal prolapse

- Children with failure to thrive, poor growth and weight gain, nutritional problems, chronic diarrhea, or malabsorption. Pancreatic insufficiency should also lead to consideration of Shwachman-Diamond syndrome.
- Children with refractory asthma (particularly at a young age), recurrent pneumonia, recurrent sinusitis, and/or nasal polyps. Alternatively, such children may have a spectrum of disorders not related to CF, including immunologic abnormalities, ciliary dysfunction, broncopulmonary anatomic abnormalities, and allergies. Though they may be present as sequelae of any of these conditions, gastroesophageal reflux and chronic tracheal aspiration also deserve to be considered as primary causes of such symptoms.
- Adolescents or adults with recurrent pancreatitis
- Adults with recurrent sinusitis/bronchitis or bronchiectasis, nasal polyps, recurrent pancreatitis, and male infertility

Recent investigations have shown that factors other than mutations in the *CFTR* gene can produce CF-like phenotypes that are clinically indistinguishable from non-classic CF caused by *CFTR* mutations [Groman et al 2002].

Congenital absence of the vas deferens accounts for 1.2-1.7% of male infertility. CBAVD is part of the differential diagnosis of obstructive azoospermia, caused by obstruction to sperm outflow from the testes or ductular system. CBAVD may be part of a syndrome or may be an isolated finding.

Approximately 80% of men with CBAVD have at least one mutation in *CFTR* [Mak et al 1999]. Syndromes with obstructive azoospermia include the following:

- Young syndrome, a progressive obstruction of the epididymis by inspissated secretions in males with chronic sinopulmonary infection [Handelsman et al 1984]. Males with Young syndrome do not have malformations of the vas deferens or epididymis.
- Hereditary urogenital adysplasia, an autosomal dominant disorder of variable expressivity and reduced penetrance. Females have a range of uterine anomalies; males may have Wolffian duct anomalies including unilateral or bilateral absence of the vas deferens; males and females may have unilateral or bilateral renal agenesis [Biedel et al 1984].

Management

Cystic Fibrosis

Referral to a regional CF center is strongly recommended for individuals known to have CF or those in whom the diagnosis is being considered. A local CF clinical care center can be identified by contacting the CF Foundation . Most individuals followed at a CF Center are evaluated quarterly by a multidisciplinary team consisting of physicians, nurses, respiratory therapists, dieticians, social workers, and genetic counselors. Epidemiologic data show that affected individuals followed on a regular basis in accredited CF centers have improved clinical outcome [Johnson et al 2003].

Respiratory. Affected individuals are regularly followed with pulmonary function

studies, chest radiographs, and specific blood and urine laboratory tests. Intervention to treat or prevent pulmonary complications may include oral, inhaled, or IV antibiotics, bronchodilators, anti-inflammatory agents, mucolytic agents, and chest physiotherapy (postural drainage with chest percussion) [Ramsey et al 1999 , Gibson et al 2003]. New therapies for the treatment of cystic fibrosis lung disease that span the pathophysiologic cascade of CF are being investigated. Additional research focuses on CFTR "bypass" therapy to augment alternative chloride channels (i.e., UTP), CFTR "protein assist" treatment to improve the trafficking and function of defective CFTR protein (i.e., butyrates), new anti-inflammatory agents, new IV and inhaled antibiotics, and antiproteases. Lung or heart/lung transplantation is an option for selected individuals with severe disease. Nasal/sinus symptoms may require topical steroids, antibiotics, and/or surgical intervention.

Gastrointestinal. Nutritional therapy may include special formulas for infants to enhance weight gain through improved intestinal absorption, supplemental feeding to increase caloric intake, and additional fat-soluble vitamins and sometimes zinc to prevent the development of deficiencies. Among individuals followed at CF centers in the US, about 18% receive routine nutritional supplementation, usually via an indwelling gastric feeding catheter [CFF Patient Registry 2002]. Pancreatic insufficiency is treated with oral pancreatic enzyme replacement with meals. Individuals may develop CF-related diabetes mellitus during teenage years or later. Though this form of diabetes is distinct from both juvenile-onset (type I) and adult-onset (type II) diabetes mellitus, some individuals do require routine insulin therapy for optimal management. Input from endocrinology consultants in the management of CF-related diabetes is recommended. Biliary sludging or frank obstruction, and associated hepatic inflammation, are treated with oral ursodiol. There are also increased risks of osteopenia related to Vitamin D and calcium deficiencies that require screening of bone density starting in adolescence.

Pregnancy. The survival of individuals with CF has improved considerably over the past few decades. Currently, the average median survival is approximately 33 years and pregnancy in individuals with CF has become an important issue. Early reports of such pregnancies were discouraging. Historically, the predictors of poor pregnancy outcome for mother and/or fetus have been a forced vital capacity (FVC) of less than 50% of the predicted value and poor nutritional status. In fact, an FVC of less than 50% of the predicted value was an absolute contraindication to pregnancy. However, with increasingly better pulmonary treatment, aggressive management of infections with a greater variety of antibiotics, and improved nutrition, pregnancies today are well tolerated, especially in women with mild to moderate disease [Edenborough et al 2000 , Gilljam et al 2000 , Gillet et al 2002]. In these women, the risk factors for deteriorating health and early death after pregnancy are the same as the nonpregnant adult population. In a more recent study, Goss et al (2003) adjusted for FEV(1) percent predicted, weight, height, and pulmonary exacerbation rate per year and found that pregnancy was not associated with an increased risk of death. In fact, pregnancy did not appear to be harmful even in a subset of individuals with diabetes mellitus or with FEV(1) less than 40% of predicted. Important predictors of pregnancy outcome the fetus are the severity of maternal pulmonary impairment and nutritional status in that deterioration during pregnancy may precipitate preterm delivery.

Ideally, a woman with CF of reproductive age should receive preconception counseling

and take steps to optimize her health prior to pregnancy. The management of pregnancy for a woman with CF requires a multidisciplinary team approach that includes a dietician, members of the CF team, and an obstetrician. Maternal nutritional status and weight gain should be monitored and optimized aggressively, pulmonary exacerbations should be treated early, and early screening for diabetes mellitus is recommended. The risk for congenital anomalies in the fetus is not increased over background. Breastfeeding is possible.

Congenital Bilateral Absence of the Vas Deferens

The main issues relate to management of infertility that results from obstruction of sperm outflow through the ductular system. Assisted reproductive technologies (ART) can be used to manage infertility. These include microscopic sperm aspiration from the epididymal remnant in conjunction with in vitro fertilization or artificial insemination using donor sperm.

Gene therapy. Gene therapy is in a research phase only. Gene therapy is not able to control or treat the symptoms related to CF at this time.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

CFTR-related disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband with cystic fibrosis

- The unaffected parents are obligate carriers (heterozygotes) and have an alteration in one copy of the *CFTR* gene.
  - If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test parents by molecular genetic testing.
- Carriers are asymptomatic.
- On rare occasions, a parent may be diagnosed as affected subsequent to the diagnosis of the child.

Sibs of a proband with cystic fibrosis

- At conception, each full sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of

being unaffected and not a carrier.
    - If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test sibs by molecular genetic testing. Otherwise, sweat chloride testing should be performed.
- For an at-risk sib who is known to be unaffected but has not yet undergone molecular genetic testing, the risk of being a carrier is 2/3.
    - If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test sibs by molecular genetic testing.
- Carriers are asymptomatic.

Offspring of a female proband with cystic fibrosis

- Females with CF are fertile.
- A woman with CF transmits one disease-causing *CFTR* allele to each of her children.
- The risk that her child will inherit a second disease-causing *CFTR* allele depends upon her partner's carrier status. *CFTR* molecular genetic testing should be offered to her partner to determine his carrier status. The specific molecular genetic testing panel that is used should be based on a partner's ethnicity and family history.
    - If the partner is a carrier, the offspring will be at risk for CF or CBAVD

Offspring of a male proband with cystic fibrosis

- Males with CF may conceive children through assisted reproductive technologies (ART).
    - An affected male will transmit one mutant *CFTR* allele to each of his offspring.
    - The risk that his child with inherit a second disease-causing *CFTR* allele depends upon his partner's carrier status. *CFTR* molecular genetic testing should be offered to his partner to determine her *CFTR* carrier status. The specific molecular genetic testing panel that is used should be based on the partner's ethnicity and family history.
    - If the partner is a carrier, the offspring will be at risk for CF or CBAVD

Parents, sibs, and offspring of a proband with CBAVD

- Males with CBAVD may conceive children through assisted reproductive technologies (ART).
- The risk for the relatives of a proband with CBAVD depends on the parental genotypes and cannot readily be predicted without this information.
- Molecular genetic testing is most informative when the CBAVD-causing *CFTR* alleles have been identified in the proband. Men with CBAVD typically have only one identifiable *CFTR* mutation, complicating the testing and interpretation of results in their family members.

Other family members. The brothers and sisters of a known *CFTR* mutation carrier each have a 50% risk of being a carrier. Even if the carrier has no known affected sibs, a residual risk remains that both parents could be carriers and thus could conceive an affected offspring.

Carrier Detection

The following situations may arise when carrier detection is pursued for at-risk relatives of individuals with CF or CBAVD and their reproductive partners:

- **Both disease-causing alleles of a proband are known.** If both disease-causing alleles have been identified in the proband, the at-risk maternal and paternal relatives can be tested for their family-specific mutation following genetic counseling.

- **Only one disease-causing allele of a proband is known.** As mutation detection rates improve, one should consider performing additional molecular genetic testing for identifiable mutations in probands. Molecular genetic testing should be informative for relatives related through the parent with the identifiable mutation. Molecular genetic testing will not be informative for relatives related through the carrier parent who does not have an identifiable mutation if the relatives are only tested for mutations in the proband's test panel. Linkage analysis may be helpful for these relatives.

- **Neither disease-causing allele of a proband is known.** As mutation detection rates improve, one should consider performing additional molecular genetic testing for identifiable mutations in probands. Molecular genetic testing of relatives will not be informative if the relatives are only tested for mutations in the proband's test panel. Linkage analysis may be helpful for these relatives.

- **The proband is deceased and no DNA testing was performed.** Under such circumstances, it is appropriate to attempt to obtain any available tissue samples for the purpose of DNA extraction and *CFTR* molecular genetic testing. If DNA cannot be obtained, it is appropriate to test at-risk family members, following genetic counseling . Those family members who have a disease-causing *CFTR* mutation are carriers and follow-up genetic counseling regarding molecular genetic testing of partners and pregnancy risks is appropriate. Those family members who do not have a mutation detected using a panel of *CFTR* mutations can have their carrier risk reduced, though not eliminated, using Bayes Theorem (Table 6). (See also the National Society of Genetic Counselors statement on carrier testing for cystic fibrosis.)

Table 6. Residual Risk (%) of a Relative Being a *CFTR* Mutation Carrier if Molecular Genetic Testing Does Not Detect a Mutation

Prior Risk of Being a Carrier	Mutation Detection Rate (%)									
	30%	40%	50%	60%	70%	75%	80%	85%	90%	95%
2/3 (66.7%)[1]	58.3%	54.5%	50.0%	44.4%	37.5%	33.3%	28.6%	23.1%	16.7%	9.1%

1/2 (50.0%) [2]	41.2%	37.5%	33.3%	28.6%	23.1%	20.0%	16.7%	13.0%	9.1%	4.8%
1/4 (25.0%) [3]	18.9%	16.7%	14.3%	11.8%	9.1%	7.7%	6.3%	4.8%	3.2%	1.6%

1. Unaffected sib of a proband
2. Unaffected sib of a carrier
3. Unaffected cousin of a proband

Click here for residual risk of being a carrier for other values of prior risk.

- **Cis configuration and trans configuration of 5T variant with a disease-causing allele is not known.** Additional family members may need molecular genetic testing to establish phase for informative interpretation of results.

- **A person has a reproductive partner who is a known carrier or is at risk based on family history.** At-risk partners should be offered *CFTR* molecular genetic testing. It is appropriate to offer molecular genetic testing to the reproductive partners of those who are found to be carriers, with the understanding that failure to detect a mutation reduces, but does not eliminate, the risk of being a carrier (See Table 7).

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

Population screening. Screening for CF carrier status is being offered to some couples as part of routine prenatal care in some centers [Grody 1999] (see Statements and Guidelines Regarding Genetic Testing). The ACMG Subcommittee on Cystic Fibrosis Screening recommends that CF carrier screening be offered to non-Jewish Caucasians and Ashkenazi Jews, and made available to other ethnic and racial groups through appropriate counseling regarding risks, testing options, detection rates, and informed consent. The Committee recommends use of a pan ethnic, 23-mutation panel that includes the majority of CF-causing mutations with an allele frequency of greater than 0.1% in the general US population (Table 8) [Watson et al 2004]. Screening panels may be supplemented with other mutations to improve sensitivity for specific ethnic groups. Implementation of population-based newborn screening programs for CF generally includes plans to address increased demands on genetic counseling resources.

5T/TG tract. The 5T/TG tract analysis should not be included in a routine carrier screen. It is an appropriate test in males with CBAVD or suspected CBAVD, individuals with non-classic CF, or adult carriers of 5T who wish to further define their reproductive risks. 5T/TG tract analysis can increase or decrease risk, but no specific risk figures are associated with test results.

Residual risk after carrier testing. Individuals with no family history of CF who test negative for a panel of *CFTR* mutations can have their carrier risk reduced (though not

eliminated) based on their ethnicity. The residual risk of being a carrier depends upon the carrier frequency and the mutation detection rate. Table 7 provides calculations of residual risk based upon the mutation detection rate of the test method used and the individual's a priori risk of being a carrier. For example, an individual with no known family history of CF has a 1/30 a priori risk of being a carrier. If the individual does not have one of the mutations in a test panel with a mutation detection rate of 95%, his/her (residual) risk of being a carrier is 1/500.

Table 7. Residual Risk (%) of an Individual with No Family History of a *CFTR*-Related Disorder of Being a *CFTR* Mutation Carrier if Molecular Genetic Testing Does Not Detect a Mutation

Prior Risk of Being a Carrier	Mutation Detection Rate									
	30%	40%	50%	60%	70%	75%	80%	85%	90%	95%
1/28 (3.57%)	2.5%	2.2%	1.8%	1.5%	1.1%	0.9%	0.7%	0.6%	0.4%	0.2%
1/60 (1.7%)	1.2%	1.0%	0.8%	0.7%	0.5%	0.4%	0.3%	0.3%	0.2%	0.1%

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

High-risk pregnancies. Prenatal testing for pregnancies at increased risk is possible by molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing mutations of the *CFTR* gene must be identified in both parents before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation diagnosis using embryonic cells is available to couples at 25% risk of having a child with CF when the disease-causing mutations of the *CFTR* gene have been identified in both parents. Pregnancy is achieved through assisted reproductive technology and requires coordination with specialists in fertility and endocrinology.

Indeterminate-risk pregnancies. In cases in which one parent is known to be a *CFTR* mutation carrier and the other parent has tested negative for a panel of *CFTR* alleles, no additional testing to clarify the status of the fetus is available. Although Girodon-Boulandet et al (2000) have suggested that assay of intestinal enzyme levels in amniotic fluid may be informative, these tests are not available in the United States and lack specificity and sensitivity.

Low-risk pregnancies. The finding of fetal echogenic bowel and/or dilated bowel on ultrasound examination is associated with an increased risk for CF in a pregnancy previously not known to be at increased risk for CF. The risk for CF may be 2-3% with Grade 2 (moderate) echogenic bowel. For Grade 3 (severe) echogenic bowel, defined as echogenicity similar to or greater than that of surrounding fetal bone and/or intestinal dilation, the reported incidence of CF has been 5-20% [Corteville et al 1996 , Slotnick & Abuhamad 1996 , Ghose et al 2000]. In this situation, genetic counseling of the parents regarding the risk for CF is appropriate, followed by *CFTR* molecular genetic testing on the parents and/or the fetus, depending on the gestational age of the pregnancy and the decision of the parents. Based on the mutation detection rate of the test method used, risk for CF when only one disease-causing allele is identified in the fetus can be calculated [Bosco et al 1999 , Hodge et al 1999].

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —ED.

Molecular Genetics of CFTR-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
CFTR	7q31.2	Cystic fibrosis transmembrane conductance regulator

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

OMIM Entries for CFTR-Related Disorders

219700	CYSTIC FIBROSIS; CF
277180	VAS DEFERENS, CONGENITAL BILATERAL APLASIA OF; CBAVD
602421	CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR; CFTR

Genomic Databases for CFTR-Related Disorders

Gene Symbol	Locus Specific	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
CFTR	*CFTR*	602421	CFTR	*CFTR*	120584	*CFTR*

For a description of the genomic databases listed, click here.

Molecular genetic pathogenesis. CFTR forms a regulated cell membrane chloride channel.

Normal allelic variants: 230 kilobases, contains 27 coding exons, produces a 6.5-kb mRNA product

Pathologic allelic variants: Over 1000 mutations are known; almost all are point mutations or small (1-84 bp) deletions. The most common mutation is ΔF508, accounting for about 30-80% of mutant alleles depending on the ethnic group. Table 8 lists the panel of 23 alleles recommended by the American College of Medical Genetics for routine diagnostic and carrier testing [Watson et al 2004]. Table 9 lists ten of the most common *CFTR* mutations and shows their most typical phenotypic effect when present in affected individuals.

Table 8. Recommended Core Mutation Panel for General Population CF Carrier Screening

3120+1G>A	A455E	G85E	R334W	1717-1G>A
3659delC	ΔF508	R347P	1898+1G>A	3849+10kbC>T
ΔI507	N1303K	R553X	2184delA	621+1G>T
G542X	R1162X	R560T	2789+5G>A	711+1G>T
G551D	R117H	W1282X		

Table 9. Ten Most Common *CFTR* Mutations in Caucasians with Related Phenotypic Expression

Mutation	Relative Frequency	Mutation Functional Class [1]	Phenotype
ΔF508	66.0%	II	Classic
G542X	2.4%	I	
G551D	1.6%	III	
N1303K	1.3%	II	
W1282X	1.7%	I	
R553X	0.7%	I	
621+1G>T	0.7%	I	
1717-1G>A	0.6%	I	
R117H	0.3%	IV	Non-classic

R1162X	0.3%	Not clear [2]	Classic

Based on www.genet.sickkids.on.ca and McKone et al (2003)
1. See Table 10 below.
2. Transcript is stable; truncated protein is probably misfolded; therefore, likely Class II.

Normal gene product: Cystic fibrosis transmembrane conductance regulator (abbreviated CFTR), a 1480-amino acid integral membrane protein that functions as a regulated chloride channel in epithelia.

Abnormal gene product: Mutations can affect the CFTR protein quantitatively, qualitatively, or both. Table 10 provides one classification scheme for the functional consequences of *CFTR* mutations [Zielenski et al 1995].

Table 10. Classification Scheme for *CFTR* Mutations

Mutation Class	Effect of Mutation on CFTR Protein	Mechanisms
I	Reduced or absent synthesis	Nonsense, frameshift, or splice-junction mutations
II	Block in protein processing	Missense mutations, amino acid deletions
III	Block in regulation of CFTR chloride channel	Missense mutations
IV	Altered conductance of CFTR chloride channel	Missense mutations

After Zielenski & Tsui 1995 and Welsh et al 2001

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

- **Canadian Cystic Fibrosis Foundation**
  2221 Yonge Street, Suite 601
  Toronto, Ontario
  Canada M4S 2B4
  Phone: 800-378-2233 (Toll free from Canada only); 416-485-9149
  Fax: 416-485-0960
  Email: info@cysticfibrosis.ca
  www.ccff.ca

- **Cystic Fibrosis Foundation**
  6931 Arlington Road 2nd Floor
  Bethesda MD 20814-5200

Phone: 800-FIGHTCF (800-344-4823); 301-951-4422
Fax: 301-951-6378
Email: info@cff.org
www.cff.org

- **Medline Plus**
  Cystic Fibrosis

- **National Library of Medicine Genetics Home Reference**
  Cystic fibrosis

- **NCBI Genes and Disease**
  Cystic fibrosis

- **Genetic Diseases Of Mucocilliary Clearance Consortium Registry**

  7019 Thurston Bowles Bldg CB#7248
  Chapel Hill NC 27599
  Fax: 919-966-7524
  Email: godwine@med.unc.edu
  Genetic Diseases Of Mucocilliary Clearance Consortium Registry

Resources Printable Copy

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PubMed

Published Statements and Policies Regarding Genetic Testing

- American College of Medical Genetics (2004) Statement on genetic testing for cystic fibrosis (pdf)
- National Institutes of Health (1997) Consensus statement on genetic testing for cystic fibrosis
- National Society of Genetic Counselors (1999) Statement on carrier testing for cystic fibrosis
- Society of Obstetricians and Gynecologists of Canada [Wilson et al 2002]

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Funding Support
National Library of Medicine, NIH
National Human Genome Research Institute, NIH

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